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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 17

Application Number: 09/781,117
Filing Date: February 08, 2001
Appellant(s): HILLMAN, JENNIFER L.

David G. Streeter
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 28, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bork et al., 1998, Current Opinion in Structural Biology, 8, pp.331-332.

Skolnick et al., 2000, Tibtech, 18, pp.34-39

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose a specific biological role for this protein or its significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect.

It is clear from the instant application that the protein described therein is what is termed an "orphan protein" in the art. The DNA of the instant application has been isolated because of its similarity to a known DNA. There is little doubt that, after complete characterization, this DNA and encoded protein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion".

The instant claims are drawn to an isolated nucleic acid molecule and the protein encoded thereby of as yet undetermined function or biological significance. It is clear from the instant specification that "[h]uman TIMM8b was identified in a screen for human sequences that resemble DDP [, deafness/dystonia peptide] and the yeast family of TIM mitochondrial proteins" (page 1, lines 29-30 of the instant specification). More specifically, human DDP, which is associated with human deafness dystonia syndrome, shows sequence similarity to a family of zinc-binding proteins in yeast (TIM proteins), that are involved in mitochondrial import, (page 1, third paragraph). Consequently, "[m]itochondria are involved in oxidative phosphorylation and apoptosis. Defects in oxidative phosphorylation are associated with a variety of neurodegenerative and neuromuscular diseases, including epilepsy, spasticity, stroke-like episodes, deafness and dystonia" (page 2, second paragraph). Therefore, based on the structural similarities to different known proteins with established function, it has been suggested that the TRP of the instant invention would also possess similar biological activity. Numerous publications exist on the topic of predicting protein functions from structural similarities or homology to the known proteins. It is well described in the art that amino acid structure cannot necessarily predict the function of the protein: "Knowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the

specific details of protein function" (see Skolnick et al., Box 2 on page 36 and the whole paper). Moreover, "Structural similarity does not necessarily mean a common evolutionary origin and homologous sequences may evolve into different folds (according to current classification schemes) (See Bork et al., Current Opinion in structural Biology, 1998, 8, page 332, first column, second paragraph). Thus, according to the state of the art, functional characteristics of a protein cannot be unequivocally extrapolated from its structural characteristics.

In the absence of knowledge of the biological significance of this specific nucleic acid and encoded protein, there is no immediately obvious patentable use for the polynucleotide or the encoded protein. According to the instant specification "cDNA encoding TIMM8b-related protein (TRP) [...] is useful in the diagnosis and treatment of cancer, particularly breast cancer, ovarian cancer, and kidney cancer; and neurodegenerative disorders, particularly Mohr-Tranebjaerg syndrome, epilepsy, spasticity, and dystonia" (page 2, lines 17-20 of the instant specification). The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that the instant nucleic acid or encoded protein is associated with any diseases or disorder. To employ the DNA and the protein in the methods generation of antibodies or diagnostic assays (see page 4, lines 15-26) is not a "real world" because it would relate to a protein for which no specific biological function is known. The instant application also fails to demonstrate use of the protein as a marker for any disease or condition (which would be a real world use). Because the instant specification does not teach a biological activity of the protein, one cannot prevent or treat a condition or disease as implied by the specification. To employ a nucleic acid of the instant invention in any of the disclosed methods would clearly be using it as the object of further research, which has been determined

by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the encoded protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

Appellant traverses the rejection for lack of utility on the premise that the instant TRP is "a member of the class of DDP related mitochondrial import proteins (DDP/TIM), whose biological functions include the import of certain transmembrane carrier protein" (page 5, first paragraph of the Appeal Brief), and, therefore, "the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease". Appellant further summarizes the Court's position on the utility requirement at pages 6-8 of the Brief. Appellant's review of the issue of utility, the case law that has been cited and the holding that is found in that case law is not disputed. The only point of disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

Beginning at page 8, Appellant argues that the invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug discovery and disease diagnosis through gene expression profiling, and that these uses are explained in the Bedilion Declaration.

The Declaration of Dr. Tod Bedilion under 37 CFR 1.132 filed May 28, 2003 is not timely, and, therefore is not considered. See 37 C.F.R. § 1.195 Affidavits or declarations after appeal (Affidavits, declarations, or exhibits submitted after the case has been appealed will not be admitted without a showing of good and sufficient reasons why they were not earlier presented).

At page 10 of the Appeal Brief, Appellant states that "the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays", and that "Given the fact that the claimed polynucleotides are known to be expressed, their utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight." This argument has been fully considered but is not deemed persuasive. First, the Examiner notes that the term "highly specific" in this context indicates that the hybridization would be highly specific, that is, that the sequence could be used to detect an exactly identical sequence. However, that is not the same thing as "specific" in the context of establishing utility; *any* sequence, regardless of origin or function, can be used in such a "highly specific" manner to detect a matching sequence; however, this is the very definition of a non-specific utility. A non-specific utility is a utility that can be attributed to any and all members of a class of compounds. In this case, the use for "specific" hybridization or detection can be performed with any nucleic acid. Appellant's analogy to a scale is inaccurate. Using the analogy to a scale, the Examiner would argue that it is the microarray that is analogous to a scale, as a scale may be used to

measure the mass of any desired object, and a microarray may be used to detect the presence of any desired nucleic acid sequence. However, the fact that a scale is useful does not confer utility on any and all objects that might be weighed using that scale, and the fact that the microarray may have utility does not confer utility on any and all nucleic acids that might be measured using the microarray. It remains that Appellant has disclosed no features or characteristics of the claimed SEQ ID NO: 2 that would inform the experimenter as to what the significance of detecting that particular sequence would be. As stated above, detection of SEQ ID NO: 2 under specific conditions using the claimed microarray would merely be an invitation to experiment further to determine what that result means, e.g. what significance the result has. Such an invitation to further experimentation does not meet the utility standard of 35 U.S.C. § 101.

Beginning at the last line of page 11, Appellant cites several "Literature review published shortly after the filing of the Hillman'117 application describing the state of the art", and that such confirm, for example, that the claimed invention is useful for differential expression analysis, regardless of how expression is regulated". The Examiner notes that these references, e.g. Rockett et al. and Lashkari et al. have not been previously cited or discussed on the record, nor have they been made of record by Appellant in any information disclosure statement. The Rockett et al. paper (Xenobiotica 1999, 29(7):655-691), however, supports the Examiner's assertion that the use of the claimed nucleic acids in microarrays does not meet the requirement of being specific and substantial. In the abstract of the paper, Rockett et al. state "An important feature of the work of many molecular biologists is identifying which genes are switched on and off in a cell under different environmental conditions or subsequent to xenobiotic challenge. Such information has many uses, including the deciphering of molecular pathways and

facilitating the development of new experimental and diagnostic procedures" (emphasis added.). In essence, Rockett et al. disclose that the purpose of such "open" microarrays, wherein the function of the specific nucleic acids is unknown, as is the case for SEQ ID NO: 2, is that the results of the experiment are to be used to decipher molecular pathways, and facilitate the development of other experimental or diagnostic procedures. Such would seem to the Examiner to clearly fall under the category of use for further experimentation to determine the properties of that which is being claimed, in this case the further experimentation being to develop other procedures that would take advantage of the knowledge gained by the initial experiment, or to 'decipher' molecular pathways. Thus, it is clear from Rockett et al. that, as asserted above by the Examiner, that the use of the claimed polynucleotides in either microarrays or in gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself; if the results of such experiments demonstrated that the claimed sequences were or were not present under particular conditions, such would be an invitation to experiment to determine why, which would fall under the aegis of further experimentation to determine the properties of that which is being claimed. Similarly, the Lashkari et al. publication does not support Appellant's assertions: While Lashkari et al. indeed teach that "amplicons", or portions of DNA amplified from the genome by PCR can be used by arraying onto glass for expression analysis, the entire context of the article has been ignored by Appellant. The very first paragraph of the paper states "This massive and increasing amount of sequence information allows the development of novel experimental approaches to identify gene function." The paragraph bridging the columns of that page starts "Experimental analysis must be performed to thoroughly understand the biological function of a gene product." The same paragraph states "it is clear

that novel strategies are necessary to efficiently pursue the next phase of genome projects-whole-genome experimental analysis to explore gene expression, gene product function, and other genome functions (emphasis added)." Thus, Lashkari et al. clearly teach that sequences of unknown function or significance are used in such strategies to learn more about the sequences themselves and the genes they represent. The Examiner maintains the position that this is clearly represents further research of the type that is not sanctioned as fulfilling the requirements of 35 U.S.C. § 101.

Appellant argues at pages 13-15 that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed individually, in that the facts and issues directed to each use are distinct and separable. First, Appellant argues that toxicology testing is a well-established utility, therefore, because the claimed polynucleotides could be used in this manner, the claimed invention possesses utility. Appellant is not incorrect in the conclusion that toxicology is a well-established use of polynucleotides and the polypeptides encoded. However, as indicated at page 13 of the Brief, "all expressed genes have utility for toxicology screening". Therefore, this is a utility, which is nonspecific and would apply to virtually every member of a general class of materials, such as proteins or DNA. While this may be a well-established use of polynucleotides, it is not a well-established, specific, substantial and credible utility of the claimed invention. Use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. If the expression of Appellant's polynucleotide of SEQ ID NO: 2 is affected by a test

compound in an array for drug screening, what useful information has been gained regarding a specific and substantial utility for SEQ ID NO: 2 as an individually claimed entity?

Appellant submits at page 14-15 of the Brief that because TRP of the instant invention displays structural similarity to "another polypeptide of unquestioned utility TIMM8b", then the instant TRP also has utility. This argument has been fully considered but is not deemed persuasive for the following reasons. As it is clearly stated in the instant specification, pp.1-2, TRP of the instant invention is TIMM8b-related protein. It is also clear from the instant specification that what is known about TIMM8b proteins is that they resemble DDP and the yeast family of TIM mitochondrial proteins, and that "[t]he human homologue of Tim8 is encoded by the DDP1 (deafness/dystonia peptide) gene, which is associated with the Mohr-Tranebjaerg syndrome, a progressive neurodegenerative disorder leading to deafness". The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that TRP of the instant invention, which has 85% sequence identity to TIMM8b protein, which in turn has some limited homology to the protein encoded by the gene associated with the Mohr-Tranebjaerg syndrome, would also be associated with the Mohr-Tranebjaerg syndrome or have any functional resemblance to the protein encoded by that gene. One skilled in the art readily understands that based on the structural similarities, TRP of the instant invention is related to TIMM8b proteins. However, these structural similarities are not equivalent to direct extrapolation of biological functions.

Appellant's argument of the use of databases containing nucleic acid sequence information at page 16 of the Brief is noted, but is not deemed persuasive, as it is the nucleic

acids themselves which are being claimed, and not a database, which is an informational representation.

At page 17 of the Brief, Appellant argues that a patent application can specify a utility without any knowledge as to how or why the invention has that utility. This argument is not disputed, but Appellant should note that the utility must also be specific, substantial and credible. Appellant's assertion that the claimed invention has utility in toxicology testing, drug development and disease diagnosis, as well as in regulation of connective tissue have all been identified as utilities which are not specific, substantial and credible, and therefore, do not meet the requirement of 35 U.S.C. § 101.

Also at page 17, Appellant argues that the biological role or function of an expressed polynucleotide is not required to demonstrate utility. This argument is also not disputed. While not required by any statute or rule, if Appellant had disclosed a biological role or function of the claimed nucleic acids or the proteins encoded thereby, such might support a disclosed utility, such as for diagnosis or treatment of disease. However, no such role has been disclosed. This alone is not probative of lack of utility under 35 U.S.C. § 101, but is merely one of the analyses, which must be made. If there were another specific, substantial and credible utility disclosed for the claimed nucleic acids, that would, in the absence of any knowledge of the biological function or role of the claimed nucleic acids, be sufficient to establish utility. However, that is not the case here.

Appellant urges at page 18 that because a set of compounds has a utility as a group, that each member has utility as part of that set. Use of the claimed polynucleotide in an array is only useful in the sense that the information that is gained from the array is dependent on the pattern

derived from the array, and says nothing with regard to each individual member of the array. This is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Appellant's individual polynucleotide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

At page 19, Appellant argues that because the Examiner has not demonstrated that the family of polypeptides expressed by humans has any, let alone a substantial number of useless members, that the Examiner must conclude that there is a 'substantial likelihood' that the proteins encoded by the claimed polynucleotides are useful. This argument has been fully considered but is not deemed persuasive because an invention must be useful I currently available form. 35 U.S.C. § 101 does not require that there be a substantial likelihood of utility, it requires that appellant have disclosed at least one specific, substantial and credible utility for that which is claimed. The fact that the encoded protein (and it is noted that the claims do not require the claimed nucleic acid to encode protein) would likely be eventually shown to be useful for something does not meet that burden. Determining what the protein would be useful for would constitute part of the act of invention. Utility must be in readily available form. In *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess

anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. Until some actual and specific activity can be attributed to the protein encoded by SEQ ID NO: 2 or the polynucleotide itself, the claimed invention is incomplete.

At page 20 Applicant further submits that specific and substantial asserted utility of the claimed polynucleotides lies in the field of detection and quantification of "differential expression of the polynucleotide expressing TRP" for diagnosis of disorders. Disorders associated with differential expression are asserted to include cancer, particularly breast cancer, ovarian cancer, and kidney cancer. Assertion of this utility is alleged to be supported by the data of Table 2 on page 39 of the instant specification. However, the data of Table 2 is not definite. It is not clear what is the difference in the degree of expression of TRP in cancer/normal tissue samples; some of the control results, for example, for ovary tumor, seem to be absent. One skilled in the art readily understands that in order to use the instant polynucleotides as a specific marker for a particular type of cancer, the following information must be present. An asserted marker must be either present or absent in a pathological tissue and that presence or absence must distinguish that tissue from healthy tissue. Alternatively, an asserted marker must be expressed at a specific level in a pathological sample. As such, in either case, the differential expression of a marker would allow a skilled artisan to clearly distinguish between normal and

cancer tissue. This is clearly not a pattern in the instant case. The instant specification, as filed, fails to provide any sound scientific reasoning in support of the conclusion that the instant TRP is associated with any cancer. There is also no factual evidence of record to support a conclusion that the instant TRP could be used as cancer marker.

With respect to Appellant's arguments at pages 20-22, the Examiner has no authority to comment regarding applicant's citation of the Written Description and Utility Guidelines, nor the statements by Mr. Kunin. However, it remains that Appellant has presented no specific and substantial utility for the claimed invention. The Examiner is not requiring a "unique" utility; if, for example, SEQ ID NO: 2 were shown to have identical expression patterns to a known cancer marker, or to be a surrogate for a cell protein of interest in toxicology, that would, indeed constitute utility. However, such is not the case here. Here, Appellant is urging that the use of the claimed nucleic acids in general methods which do not require any knowledge of the specific properties of the claimed nucleic acids is a specific an substantial utility, although the results of such applications would merely be useful for further research. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held the "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot

be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". The instant invention has no utility and is not enabling because one cannot, following the guidance presented therein, use the claimed protein without first making a substantial inventive contribution, that is, without determining a property of the protein that would lend itself to a specific, substantial and credible use.

In summary, Appellant's arguments would urge that any nucleic acid isolated from a human meets the utility requirement of 35 U.S.C. § 101 because such nucleic acids can be used in microarrays or in gene expression studies. The Examiner urges that while the burden of showing utility is not high, that such uses do not meet that burden, as they are not specific to the particular nucleic acid being claimed, and, as supported by the references cited by appellants in the brief, such uses merely constitute using that nucleic acids as the object of further research. The Examiner is of the opinion that granting a patent on the nucleic acid of SEQ ID NO: 2 based upon the disclosure in this application would be equivalent to granting a patent on a newly discovered chemical element; all Appellant has done is to isolate the nucleic acid; there is no *quid pro quo* in terms of having found and disclosed any use for the claimed nucleic acid that is based upon the particular properties of that nucleic acid. All Appellant has done is to isolate and characterize a nucleic acid sequence that occurs in nature, and seek patent protection in return for that isolation.

Therefore, for reasons set forth above, Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

Respectfully submitted,

Olga N. Chernyshev, Ph.D.
July 28, 2003

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